Risk Factors and Treatment Outcomes of 1,375 Patients with Testicular Leydig Cell Tumors: Analysis of Published Case Series Data

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Abstract: AIMS Leydig cell tumors (LCTs) are rare but the most common non-germ cell testicular tumors. Only limited evidence exists for reliably differentiating between benign and malignant LCTs and for optimally managing the different types and stages of this rare disease. This review aims to synthesize the available evidence regarding the clinical presentation and clinicopathological characteristics associated with LCT malignancy and management. METHODS We analyzed published case series with LCTs patients. The association between clinicopathological variables and the presence of metastatic disease was assessed using regression analyses. RESULTS We included 357 reports, reviewing available data from 1,375 patients (median age: 34y). Testis-sparing surgery (TSS) was performed in 463 patients. Local recurrence after TSS occurred in 8 of 121 (7%) patients with available follow-up information. Metastases were found in 101 patients and were most often located in the retroperitoneal lymph nodes (60%), lungs (38%), and/or liver (29%). The multivariable models with or without multiple imputation predicting metastatic disease included older age, larger tumor size, the presence of any adverse factor (larger tumor diameter, necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypia), and any protective factor (Reinke crystals, lipofuscin pigments, gynecomastia) with model AUCs of 0.93. Durable remission after resection of metastases or platinum-based chemotherapy was rarely seen. CONCLUSION Our risk tables using clinicopathological parameters can help identify patients harboring malignant tumors. These patients should undergo staging and either be followed or receive further treatment. In metastatic disease surgical and systemic treatment might result in disease control in in some patients.

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Variable	Original database		Imputed database		Consolidated variables	Original database		Imputed database	
	OR (95% CI)	p-value	OR (95% CI)	p-value		OR (95% CI)	p-value	OR (95% CI)	p-value
Age		<0.001		<0.001					
<42years	Reference		Reference						
≥42years	7.19 (4.11-12.6)		9.51 (6.21-14.56)						
Tumor size		<0.001		<0.001					
<30mm	Reference		Reference						
≥30mm	6.90 (3.36-14.2)		14.44 (9.25-22.56)						
Risk factors									
Necrosis	20.0 (6.90-57.9)	<0.001	12.75 (8.20-19.85)	<0.001					
Angiolymphatic invasion	26.9 (8.12-89.0)	<0.001	21.10 (13.03-34.16)	<0.001					
Pleomorphism	5.40 (1.37-21.3)	0.02	3.20 (2.16-4.75)	<0.001	No adverse risk factor	Reference		Reference	
High mitotic index	12.7 (5.20-31.2)	<0.001	7.36 (4.86-11.15)	<0.001	≥1 adverse risk factor	24.8 (9.57-64.2)	<0.001	8.65 (4.76-15.72)	<0.001
Atypias	22.8 (5.86-88.4)	<0.001	13.34 (8.58-20.76)	<0.001					
Protective factors									
Reinke Crystals	0.12 (0.04-0.47)	0.002	0.07 (0.04-0.13)	<0.001					
Lipofuscin	0.06 (0.01-0.42)	0.005	0.07 (0.04-0.10)	<0.001	No protective risk factor	Reference			
Gynecomastia	0.15 (0.05-0.40)	<0.001	0.24 (0.16-0.36)	<0.001	≥1 protective risk factor	0.13 (0.06-0.27)	<0.001	0.04 (0.02-0.06)	<0.001

CI: confidence interval, OR: odds ratio